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(54) Title: STANDARDIZED BOTANICAL PREPARATIONS AND METHODS FOR PREPARING SAME

(57) Abstract

Standardized botanical products, having a uniform content of marker compound from batch to batch and methods of preparing them are disclosed.

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STANDARDIZED BOTANICAL PREPARATIONS AND METHODS FOR PREPARING SAME

FIELD OF THE INVENTION

The present invention relates to standardized botanical preparations and processes for preparing these. The standardized botanical preparations have a consistent content of one or more marker substances, and are prepared by determining the amount of marker substance to be provided per unit of standardized botanical material, determining the amount of a marker substance in a particular batch of botanical material, and admixing the botanical material with a dosage modifying material to provide the standardized botanical preparation having the predetermined content of the marker substance. The standardized botanical preparations may be used to produce a variety of products with reduced batch to batch variations while maintaining the natural spectrum of ingredients contained in the botanical material.

BACKGROUND OF THE INVENTION

For centuries, mankind has employed the natural flora available in many applications. For example, plants have been used to treat, alleviate or prevent various conditions, to enhance performance and to provide preparations such as bath and beauty aids. In early times, whole plant products were employed, but crude extracts of various types were also prepared and used.

Many species of plants have been studied for medical use, and certain of their bioactive components have been identified and have become the subject of further study. Advances in science have allowed the isolation of relatively pure individual ingredients from plants, and these isolated substances are often employed as pharmaceuticals. Given the vast number of varied substances in any given plant, many of which have unknown bioactivity, as well as the difficulties presented in isolating and testing each individual

compound, one line of thought is that it is better to administer a whole plant product, such as ground roots or leaves, to obtain the benefits from the entire spectrum of naturally occurring substances in the plant, than to administer a single, purified substance.

Extracts have also been prepared from plants as a "stepping stone" to isolation or concentration of the bioactive compounds. Dosage forms made from these extracts, isolates and concentrates are commercially available. Some argue that extracts are more beneficial than whole herb preparations because the concentration of the bioactive (marker) substance or substances in the extract can be better controlled compared to batch to batch variations in the concentration of bioactive compounds that may and does occur in botanicals. Geography, soil conditions, storage conditions, and many other factors are known to contribute to the variations in content of marker compounds in batches of botanicals. Thus, the concentration of a particular marker compound in an extract will vary with the source of the extract, and batch to batch variations occur.

There are commercially available products that contain a mixture of whole plant and extract for purposes of providing a full spectrum product, but only the amount of certain marker substance or substnaces in the extract portion are controlled. Thus, the total content of marker substance of the final product will vary with the content of the active compound in a particular batch of a botanical, resulting in batches of the same product having different potencies.

In Tyler, Varro E., Herbs of Choice, page 5 (The Hawarth Press, Inc., Binghamton, NY, 1994) it has been suggested that standardized products having a defined therapeutic activity can be obtained by assaying the plant material to quantify the amount of a known constituent of a plant to determine biological activity via a bioassay. Once the potency is determined, the plant can be mixed with an appropriate quantity of material of greater or lesser potency to produce a product of specified activity. Conventionally, this has been accomplished by adding the isolated or purified substance, by adding a whole herb of a different concentration or potency, or by adding inert fillers to produce a product having the desired active ingredient content.

Despite advances in the art, improved standardized botanical products remain desirable. These products should be monitored closely and controlled to provide equipotent amounts of one or more marker substances from product to product and from batch to batch, taking into account and correcting the natural batch to batch variations found in botanicals.

The present invention overcomes the shortcomings of the botanical products of the prior art and achieves the aforementioned objects and others that will become apparent from the detailed disclosure herein.

SUMMARY OF THE INVENTION

The present invention is directed to standardized botanical preparations containing a predetermined content of a marker substance and a sufficient amount of a dosage modifying material, e.g., a natural or synthetic extract containing the marker substance, such that a predetermined amount of the marker substance is contained in a predetermined amount of the standardized botanical. Typically, the content of marker substance in the standardized botanical will be determined by the desired dose of marker substance to be delivered in the final product prepared from the standardized botanical.

The standardized botanical preparations of the present invention are prepared by determining an amount of marker substance to be contained in a botanical product, wherein at least a portion of the marker substance is provided by a botanical material, determining the amount of botanical material to be contained in the dosage form, analyzing the content of the marker substance in a sample of the botanical material, and adding a sufficient amount of a dosage modifying material to the botanical material to provide a standardized botanical having the predetermined amount of maker substance. This method yields standardized botanical products having substantially no batch to batch variation. Typically, the botanical material will be subpotent with respect to the marker substance of interest, and an extract containing the marker substance will be added as the dosage modifying material to yield a standardized botanical having the desired content of marker substance.

The present invention is also related to a method for preparing botanical products containing the standardized botanicals of the invention by determining the amount of marker substance to be contained in a botanical product, determining the amount of marker compound present in a batch of botanical material to be used to make the botanical product, preparing a standardized botanical by admixing the botanical material with a sufficient amount of a dosage modifying material such that the amount of standardized herb to be contained in the botanical product contains the predetermined amount of marker substance, and preparing the standardized botanical product containing the predetermined amount of marker compound, wherein the predetermined amount of marker compound is provided by the standardized herb. From 0 to 99%, preferably from 0.001 to 60% by weight of the standardized botanical of a dosage modifying material is admixed with the botanical material to yield the standardized botanical.

The botanical products containing the standardized botanical may be in any form, e.g., capsules, tablets, suspensions, powders, bath soaps, cooking herbs, ointments, creams, and the like.

The present invention is also directed to the prophylaxis, treatment, alleviation, termination or enhancement of biological processes by delivering an effective amount of the standardized botanical of the present invention in need thereof. It will be understood that the effective amount will differ with the individual subject and with the subject biological process. Subjects may be any animal, e.g., mammals, reptiles, insects, birds, fish, and humans.

A detailed discussion of the invention follows.

DETAILED DESCRIPTION

Standardized botanicals according to the invention are prepared from any botanical material for which a standardized botanical product is desired. The standardized botanicals of the present invention are prepared by first determining a desired content of marker substance to be included in the standardized botanical or in a botanical product, e.g., a capsule or infusion. Predetermination of the amount of marker substance will

include many factors, including the general range of potencies of marker substance, the final product to be delivered, and other factors known to the skilled artisan.

The botanical material used to prepare the standardized material may be derived from any plant, fungi, algae or part thereof such as the leaf, flower, stem, root or rhizome. The plant may be terrestrial or aquatic, and it is contemplated that certain aquatic plants such as kelp may be particularly suited for use with the present invention.

For purposes of the present invention, the term "marker substance" is any substance naturally found in a botanical which can be measured directly or indirectly by appropriate analytic techniques, e.g., bioassays, gas or liquid chromatography, ultraviolet spectrophotometry, etc. It is preferred that the marker substance exhibit a biological effect upon administration to subject. However, it is possible that the marker substance does not exhibit such activity itself but serves as a reference compound with which to measure the content of other components which do exhibit a biological effect. Marker substances may also be, for example, oils that provide flavor but do not exhibit therapeutic properties.

The term "marker substance" also includes groups of compounds in a plant, e.g., ginsenosides, that are chemically related such that their presence can be measured by a single assay. These compounds are typically considered to be the active ingredient in the botanical, but in a broader sense refer to the substance or substances of interest.

Once the marker substance of interest is determined, the amount of marker substance and other ingredients to be included in the botanical product is determined. This will vary based on a variety of factors, including the therapeutically or prophylactically effective amount of the marker substance, the disease, condition, other biological process to be treated or otherwise modified; the final size and shape of the botanical product; and other factors known to those skilled in the art.

The standardized botanical will typically be in particulate form, e.g., a powder or granules. It has been discovered that manufacture of the botanical products may be facilitated if the standardized botanicals are prepared with tap densities greater than that of the starting botanical material. The tap density is the mass of a material that, upon packing in a precisely specified manner, fills a container to a specified volume, divided by the container volume. Traditional methods of determining tap density include

repeatedly lifting and dropping a container of sample to tap down the volume and pack the particles. It is preferred that the tap density of the standardized botanical is between 0.2 and 2.0 g/cc; preferably between 0.45 to 1.0 g/cc, and most preferably between about 0.6 to 0.95 g/cc when measured using the USP23/NF18 Supplement 6 (1997) test method 616, incorporated herein by reference.

The tap density of the standardized botanical can be adjusted by additional manufacturing steps, e.g., by wet or dry granulation, spray drying or encapsulation with an encapsulation agent such as cellulose. The standardized herb may also be mixed with a binder to yield an agglomerate. The resultant product may then be milled to the desired particle size and/or tap density.

Once the amount of marker substance to be delivered in the botanical product is determined, then the botanical product must be manufactured. The botanical product may be, for example, a powder, capsule, tablet, suspension, dragee, sachet, ointment, cream, suspension, infusion or other known pharmaceutical dosage form, and the dosage forms may be immediate release, sustained release, or enteric. The botanical product can also be a food product, such as a health bar, cereal, nutritional supplement beverage, and so forth. Other suitable products include bath beads, deodorants, dusting powders, shampoos, hair conditioners, soaps, skin cleansers, facial peels, and the like. Products that are aesthetically pleasing such as potpourris and fragrances are also contemplated. The standardized herb itself may be the desired final product, and may be prepared in bulk for use in a variety of products. Thus, large batches of standardized botanical with a known amount of marker compound per unit weight may be prepared in advance for later use, providing a conveniently readily available source of material for the manufacture of the botanical products.

Once the type of botanical product to be prepared has been determined, the amount of marker substance to be contained in each product unit is determined. The content of marker substance will depend upon the particular form of the final product, the amount of marker substance to be delivered, the physical capacity of the final product, e.g., capsule volume, and other considerations which will be apparent to those skilled in the art.

The batch of botanical material to be used to prepare a batch of standardized botanical is then analyzed to determine the marker substance content. If the content is not the predetermined amount, a dosage modifying material is added to achieve the correct content of marker substance.

The dosage modifying material may be an extract containing the marker substance or an inert diluent. Typically, the dosage modifying material will be an extract. The extract may be natural or synthetic, but is preferably natural. It is preferred that the extract is prepared from the same botanical material used to prepare the standardized botanical. The dosage modifying material may be from any source, e.g., botanical, animal or synthetic.

It is contemplated that different extracts having different content of the compound can be used to achieve the desired final product.

The analytical method used to determine the amount of marker substance or unit of measure in the batch of whole herb will depend on the botanical material used, and the marker substance to be measured. Table 1, which follows, lists a variety of botanicals which may be used in accordance with the invention, and indicates the desired portion of that plant to be used, a desired marker substance contained in the plant and a preferred analytic technique for determining the content of marker substance.

TABLE 1

Herb	Plant Part Used	Method of Analysis	Analyte or unit of measure
Saw Palmetto	Berry	High Resolution Gas Chromatography	Fatty acids
Kava Kava	Rhizome	High Pressure Liquid Chromatography	Kava lactones
Green Tea	Leaves	High Pressure Liquid Chromatography	Catechin and related monomers
Green Tea	Leaves	Spectrophotometry	Total phenols by Folin-Denis method
Panax Ginseng	Root	High Pressure Liquid Chromatography	Ginsenosides

Herb	Plant Part Used	Method of Analysis	Analyte or unit of measure
Siberian Ginseng	Root	High Pressure Liquid Chromatography	Eleutherosides
St. John's Wort	Aerial plant parts; flowers and leaves	High Pressure Liquid Chromatography	Hypericin, pseudo hypericin, and related compounds
St. John's Wort	Aerial plant parts; flowers and leaves	Spectrophotometry	Total napthodianthrones
Echinacea	Flowers, leaves, stems, and root	High Pressure Liquid Chromatography	Echinacoside, cholorgenic acid, cichoric acid, and caffeoyl tartaric acid
Echinacea	Flowers, leaves, stems, and root	Spectrophotometry	Total Phenols by Folin-Ciocalteau method
Black Cohosh	Root	High Pressure Liquid Chromatography	Triterpenes
Ginkgo Biloba	Leaves	High Pressure Liquid Chromatography	Ginkgoflavone glycosides and ginkgo terpenoids
Valerian	Rhizome and root	High Pressure Liquid Chromatography	Valerenic acids
Cranberry	Berry	High Pressure Liquid Chromatography	Organic acids (Quinic, malic, citric, and shikimic acids)
Garlic	Bulb	High Pressure Liquid Chromatography	Allicin releasing potential
Grape Seed	Seed	High Pressure Liquid Chromatography	Catechin and related monomers
Grape Seed	Seed	Spectrophotometry	Porter Value Units
Ginger	Rhizome	High Pressure Liquid Chromatography	Gingerols and Shogaols
Ginger	Rhizome	Spectrophotometry	Gingerols

A sufficient amount of the dosage modifying material is added to adjust the content of the marker substance in the standardized botanical such that a unit dose of

standardized botanical containing the appropriate predetermined amount of botanical to be included in a single dosage form also contains the predetermined amount of marker substance, wherein the botanical material contributes at least a portion of the marker substance content. Inclusion of a dosage modifying material is not necessary if a unit dose of the botanical to be included in the final dosage form contains the required amount of marker substance, but it is necessary to determine the marker substance content to insure that there is no batch to batch variation.

The ratios of the standardized botanical components will vary widely, according to the desired marker compound content in the standardized herb. The important aspect is that the standardized botanical should deliver a consistent amount of marker substance per unit dose or unit of use, so that batch to batch variations can be reduced and all of the marker substance contained in the standardized herb or final dosage forms is accounted for. The standardized botanical will typically be a particulate solid and will have a weight ratio of botanical material to dosage modifying material ranging from about 99.99:0.01 to about 0.01:99.99, preferably from about 90:10 to about 10:90, and more preferably from about 60:40 to 40:60.

Once the standardized botanical is prepared, it is preferable to conduct another assay on the final product to insure the potency of the marker substance in the final product. The assay used to test the product may be the same as that used to determine the marker substance content of the botanical, or it may be different.

The standardized botanical product of the present invention can then be used to prepare final products, such as capsules, pills, tablets, soaps, shampoos, topicals, such as creams and ointments, foods such as health bars, or other forms known in the art. Capsules are a preferred dosage form. The products preferably contain a sufficient amount of the standardized botanical product to elicit a desired effect on a biological products, such as a therapeutic or prophylactic effect, an anesthetic effect, or enhancement of a biological process, e.g., virility. The dose of standardized herb, and therefore marker substance, will vary with the desired therapy, the disease or treatment to be rendered to a patient, and the like. Suitable topical products include ointments, creams, lotions, emulsions, and the like. It is also contemplated that the standardized botanical products

can be incorporated into food products and beverages, e.g., snack bars, infusions such as teas, and the like.

Compositions in accordance with the invention have unexpected efficacy in stimulating biological processes, such as, but not being limited to, cell proliferation. Compositions, including one or more of the inventive formulations alone or in combination with other materials such as vitamins, minerals, known cell proliferation stimulating agents, etc. can be used to provoke unexpectedly high proliferation rates of, e.g., T cells, macrophages, and other cells. Such an effect is useful in the development of such cells for use in therapies such as autologous transfer, as research tools, as markers for studying efficacy of therapeutic regimens, and so forth.

Other ingredients may be included in the botanical products of the present invention, such as vitamins, minerals, colorants, flavorants, lubricants, anti-oxidants, stabilizers, appropriate vehicles and the like. Certain dosage forms, e.g., tablets and capsules, may be coated with sugar or gelatin coats, sustained or enteric coatings, or the like.

The steps used to prepare the final product will vary with the product to be prepared, and will be well known to the skilled artisan. Fox example, capsules are preferred dosage forms, and are prepared by encapsulating the predetermined amount of whole herb along with the required amount of dosage modifying material such that the final capsule provides the predetermined dose of marker substance.

The following table lists some botanicals along with their medicinal uses, and typical dosage ranges.

TABLE 2

Herb	Uses	Daily dose
Saw palmetto berry	treatment of urination problems in benign prostatic hyperplasia	1-2 g berry or 320 mg lipid extract
Kava Kava	treatment of anxiety, nerves, stress	60-120 mg kava pyrones
ginseng root	fatigue	1 to 2 g root

St. John's Wort	depression	2-4 g herb or 0.2 to 1 mg hypericin
Echinacea Purpurea	colds, chronic infections	250-1500 mg standardized extract standardized to contain a minimum of 4% total phenols and cichoric acid
Black Cohosh Root	premenstrual discomfort	40 mg standardized extract (2.5% triterpenes)
Ginkgo Biloba Leaf	vertigo; disturbed performance in organic brain syndrome; improvement of pain free walking in peripheral arterial occlusive disease	120-240 mg native dry extract

It is preferred that the products of the present invention contain only organic ingredients and more preferably conform with the specifications and requirements of the Organic Foods Production Act.

The following examples are illustrative of preferred embodiments of the invention.

Comparative Example 1

This example shows the wide variation in marker substance content between different lots of a commercially available St. John's wort herb/whole herb product. Two different lots (designated herein as Lots A and B) of store bought capsules were analyzed for their hypericin content. All capsules contained 175 mg of 0.3% St. John's wort extract, and 300 mg of St. John's wort whole herb. The hypericin content of the capsules was then measured. The data show that the capsule from Lot A had a hypericin content of 0.556 mg/capsule, while the hypericin content for those of Lot B was 1.43 mg/capsule, almost a threefold difference.

Comparative Example 2

The same analysis described in Comparative Example 1 was conducted on two different lots (designated herein as Lots C and D) of another commercially available St.

John's wort preparation containing 150 mg of 0.3% hypericin St. John's wort extract, and 300 mg of the whole herb. Lot C was found to have a hypericin content of 0.345 mg/capsule, while Lot D was found to have 1.193 mg hypericin/capsule, nearly a fourfold difference.

The foregoing comparative examples show that there are wide batch to batch variations in the potency of the same commercial product.

Comparative Example 3

To further demonstrate the wide variations in herbs from different sources or different batches from the same source, or different batches of whole herb. The samples were taken from a wide variety of commercially available products, in varying doses. The following table shows the herb, the marker substance measured and the % marker in the batch of herb:

TABLE 3

Herb	Marker	% Marker in herb
Echinacea purpurea (herb)	Phenols	0.78
Echinacea purpurea (herb)	Phenols	0.78
Echinacea purpurea (herb)	Phenols	0.80
Echinacea purpurea (herb)	Phenols	0.89
Echinacea purpurea (herb)	Phenols	0.92
Echinacea purpurea (root)	Phenols	0.82
Echinacea purpurea (root)	Phenols	0.84
Echinacea purpurea (root)	Phenols	0.86
Echinacea purpurea (root)	Phenols	0.92
Green tea	Catechins	13.40
Green tea	Catechins	16.20

Herb	Marker	% Marker in herb
Green tea	Catechins	20.00
Kava kava	Kavalactones	4.30
Kava kava	Kavalactones	6.00
Kava kava	Kavalactones	6.40
Panax Ginseng	Ginsenosides	2.00
Panax Ginseng	Ginsenosides	2.40
Panax Ginseng	Ginsenosides	5.20
Siberian Ginseng	Eleuthrosides	0.07
Siberian Ginseng	Eleuthrosides	0.09
Siberian Ginseng	Eleuthrosides	0.13
Siberian Ginseng	Eleuthrosides	0.17
St. John's Wort	Hypericins	0.04
St. John's Wort	Hypericins	0.05
St. John's Wort	Hypericins	0.11
St. John's Wort	Hypericins	0.15
Valerian officinalis	Valerenic acid	0.12
Valerian officinalis	Valerenic acid	0.12
Valerian officinalis	Valerenic acid	0.12
Valerian officinalis	Valerenic acid	0.12
Valerian officinalis	Valerenic acid	0.13
Valerian officinalis	Valerenic acid	0.24

Comparative Example 4

The total phenol content of three different strengths of commercially available capsules that contain echinacea were analyzed using HPLC to determine if there were inter-batch variations in phenol content. The capsules contained 190 mg, 250 mg and 400 mg of echinacea/capsule. Samples of two different lots of each strength from the same manufacturer (designated A and B) were analyzed. Results follow:

Sample	TOTAL PHENOLS/CAP (mg)		
	190	250	400
A	6.3mg	1.76	6.0
B	4.9mg	2.6	9.1

The results show wide variation between different lots of the same echinacea capsules. Also note the wide variation of phenol content between strengths.

Comparative Example 5

The valerenic acid content of capsules from two different lots of a commercially available capsules containing 535 mg of valerian root powder were analyzed by HPLC and found to contain 0.89 mg and 0.69 mg of valerenic acid, respectively.

Comparative Example 6

Two different lots of commercially available capsules containing 150 mg of 30% standardized kava kava root extract and 150 mg of kava kava root powder were analyzed by HPLC for kava lactone content. The extract would be expected to provide 45 mg of kava lactones (150 mg x .30 = 45 mg). The analysis revealed that one lot of the capsules contained 94.5 mg kava lactones per capsule, while the other lot was found to contain 88.01 mg.

The following examples illustrate preferred embodiments of the present invention.

Example 1

Capsules containing 60 mg catechins from green tea were prepared as follows: A batch of green tea was tested and found to contain about 14.5% catechins. The capsules desired had sufficient volume to contain 950 mg of green tea material, containing both leaf and extract. To prepare the standardized herb product, a standardized green tea was prepared such that 411 mg of this product contained 410 mg of green and 1 mg green tea extract. This was encapsulated to yield a product containing 60 mg of catechins/capsule.

	410 x 0.145	=	59.4 mg of catechins
	1 x 0.60	=	0.6 mg of catechins
Total	411 mg		60 mg of catechins
Capsule Filler	439 mg		

Example 2

A batch of Black Cohosh was found to contain 0.8% triterpenes, and a Black Cohosh extract containing 2.5% triterpenes was used to prepare a standardized herb containing 0.5 mg triterpenes per 60.4 mg standardized herb. A capsule containing 0.5 mg black cohosh triterpenes was prepared. The desired capsule has sufficient volume for 100 mg of Black Cohosh material, both herb and extract. To prepare the standardized herb, a standardized herb was prepared such that 60.4 mg of standardized herb contained 59.4 mg of Black Cohosh herb and 1 mg of Black Cohosh extract and filled into capsules to provide a dose of 0.5 mg of triterpenes/capsule. Calculation are shown below:

	59.4 x 0.008	=	0.457 mg of triterpenes
	1 x 0.025	=	0.025 mg of triterpenes
Total	60.4 mg		0.5 mg of triterpenes

The extra room in the capsule was filled with inert excipient.

Example 3

A Panax ginseng standardized herb is prepared as follows: Panax ginseng containing 2.5% ginsenosides, and a typical Panax ginseng extract containing 7% ginsenosides were used to prepare the standardized herb. Seven milligrams of ginsenosides were to be included in the capsule, which has sufficient volume for 950 mg of Panax ginseng material, containing both herb and extract. Panax ginseng herb was combined with Panax ginseng 7% ginsenoside extract to yield a standardized product containing 277 mg of Panax ginseng powder and 1 mg of the Panax ginseng extract. This was filled into gelatin capsules to yield capsules having 7 mg ginsenosides. These were produced into capsule containing 7 mg of ginsenosides/capsule. Calculations are shown below:

	277 mg x 0.025	=	6.93 mg of ginsenosides
	1 mg x 0.07 =		0.07 mg of ginsenosides
Total	278 mg		7 mg of ginsenosides

Extra capsule volume was filled with inert excipient.

Example 4

Capsules containing 136 mg saw palmetto berry fatty acids was prepared by mixing Saw Palmetto herb having a fatty acid content of 18.0 % with Saw Palmetto extract having a fatty acid content of 85.0% to produce a standardized herb such that 752 mg of the standardized herb contained 751 mg of Saw Palmetto herb and 1 mg Saw Palmetto extract to provide 136 mg of fatty acids/capsule. Calculations are set forth below:

	751 mg x 0.18 =		135.15 mg of fatty acids
	1 mg x 0.85	=	0.85 mg of fatty acids
Total	752 mg		136 mg of fatty acids

Extra capsule volume was filled with inert excipient.

Example 5

St. John's Wort #1

A capsule containing 0.9 mg hypericins from St. John's Wort was prepared using a capsule having sufficient volume for 898 mg of St. John's Wort material, both herb and extract. St. John's Wort herb containing 0.1% hypericins was combined with St. John's Wort extract (0.3% hypericins), to obtain a standardized herb having 0.9 mg of hypericins/950 mg standardized St. John's Wort. Capsules containing 898 mg of the

standardized herb were prepared using conventional techniques. The calculations are shown below:

897 x 0.001	=	0.897 mg of hypericins
1 x 0.003	=	0.003 mg of hypericins
Total 898 mg		0.9 mg of hypericins

The extra capsule volume was filled with inert excipient.

Example 6

St. John's Wort #2

Capsules containing 0.9 mg hypericins from St. John's Wort were prepared as follows: St. John's Wort containing about 0.1% hypericins was combined with St. John's Wort extract containing 0.3% hypericins was combined with St. John's Wort Herb to provide a product having 0.9 mg hypericins. The capsule had room for 480 mg of St. John's Wort material, containing both herb and extract. The capsules were prepared by encapsulating 480 mg of the standardized St. John's Wort to yield capsules having 0.9 mg of hypericins per unit dose standardized St. John's Wort product is produced; the calculations are shown below:

270mg herb x 0.001	=	0.27 mg of hypericins
210 mg extract x 0.003	=	0.63 mg of hypericins
Total 480 mg		0.90 mg of hypericins per capsule

Extra volume in the capsule was be filled with inert excipient.

Examples 7 to 10

In Examples 7 to 10, dosage forms containing different amounts of kava lactones are prepared.

Example 7

Capsules containing 48 mg kava lactones are desired, and the capsule has sufficient volume to contain 625 mg of kava kava material, both powdered root and extract. To prepare capsules, kava root found to contain 4.8 kava lactones is combined with kava extract (10% kava lactones) to produce a product having 48 mg of kava lactones per 625mg of the standardized kava product. Calculations are shown below:

	279 x 0.048	=	13.4 mg of kava lactones
	346 x 0.10	=	34.6 mg of kava lactones
	Total 625 mg		48 mg of kava lactones per capsule

Example 8

Capsules containing 61.2 mg kava lactones were prepared in a capsule having sufficient volume to contain 625 mg of kava kava material, containing both powered root and extract. Kava root containing 4.8% kava lactones was combined with kava extract having 30% kava lactones to produce a standardized herb containing 61.2 mg of kava lactones per 625 mg of the standardized kava product. Calculations are set forth below:

	553.6 x 0.048	=	26.6 mg of kava lactones
	71.4 x 0.30	=	34.6 mg of kava lactones
	Total 625 mg		61.2 mg of kava lactones per capsule

Example 9

Capsules containing 48 mg kava lactones were prepared using capsules having sufficient volume to contain 625 mg of kava kava material, containing both powered root and extract. Kava root having 4.8% kava lactones and was admixed with kava extract having 50% kava lactones to yield a standardized product having 48 mg of kava lactones per 625 mg of the standardized kava product. Calculations are shown below:

	585.2 x 0.048	=	28.1 mg of kava lactones
	39.8 x 0.50	=	19.9 mg of kava lactones
Total	625 mg		48 mg of kava lactones per capsule

Example 10

Capsules containing 48 mg kava lactones/capsule were prepared using a capsule that has sufficient volume for 625 mg of kava kava material, containing both powdered root and extract. Kava root containing 4.8% kava lactones was combined with kava extract having 70% kava lactones to obtain a standardized product having 48 mg of kava lactones per 625mg standardized product. Calculations follow:

	597.4 x 0.048	=	28.7 mg of kava lactones
	27.6 x 0.70	=	19.3 mg of kava lactones
Total	625 mg		48 mg of kava lactones per capsule

Examples 11-14

In the following examples, St. John's Wort preparations were prepared from various batches of St. John's Wort herb and the same 0.3% hypericin extract using the methods described in the examples shown above. The calculations are shown below:

STANDARDIZED ST. JOHN'S WORT PREPARATIONS

	Ex. 11	Ex. 12	Ex. 13	Ex. 14
% Marker in Herb (wt.%)	0.04	0.05	0.11	0.15
% Marker in Extract (wt.%)	0.3	0.3	0.3	0.3
Total weight available (mg)	480	480	480	480
mg of Marker in capsule (mg)	0.9	0.9	0.9	0.9
Weight of herb needed (mg)	207.69	216.00	284.21	360.00
Weight of extract needed (mg)	272.31	264.00	195.79	120.00
Marker in herb (mg)	0.083	0.108	0.313	0.54
Marker in Extract (mg)	0.817	0.792	0.587	0.36
Total Marker (mg)	0.9	0.9	0.9	0.9

Example 15

This example shows the advantage of increased tap density. Capsules may prepared to contain 0.9 mg hypericin from St. John's Wort. The density of the St. John's Wort herb will be 0.6 g/cc, and the capsule is filled with 600 mg extract and herb. With a hypericin level of 0.1% in the herb and 0.3% in the extract, 150 mg extract and 450 mg herb powder were required to provide 0.9 mg hypericin.

Using a density of 0.85 g/cc and the same level of hypericin, the same capsule can be filled with 824.5 mg of herb powder and only 25.5 mg of extract.

Example 16

A product containing Gingko Biloba and additional ingredients is required to provide 14.4 mg of Ginkgo flavone glycosides. If the tap density is 0.6 g/cc, 56 mg extract and 158 mg herb powder is required. If the tap density is 0.9 g/cc, the same level of marker can be delivered by only 48.4 mg extract and 464 mg herb powder.

Example 17

A capsule is prepared having the formulation shown below:

Echinacea Standardized Herb (3.5% total phenols)	350 mg
Ascorbic Acid 95%	90 mg
Zinc gluconate (12% zinc)	7.5 mg
Arabinogalactan	250 mg

The ingredients are mixed and filled in 00 gelatin capsules. The tap density of the Echinacea standardized herb, which was prepared according to the methods described above, is 0.75 g/cc or greater.

Dicalcium phosphate, rice flour, stearic acid, magnesium stearate and silicon dioxide may be added as excipients.

Example 18

Ginseng capsules were prepared having the formulation set forth below:

INGREDIENT	mg/cap
Panax Ginseng Standardized Herb 2.7% ginsenosides	280.5 mg
Siberian Ginseng Standardized Herb (0.22% eleutherosides E&B)	514.5 mg
Coenzyme Q (8% ubiquinone)	5 mg
Vitamin B12	15 mcg
Vitamin E (dry 700 IU/g d-alpha tocopherol acetate)	5 IU

The Panax Ginseng and Siberian Ginseng Standardized Herbs were prepared according to the methods described above.

The ingredients were mixed, with excipients if necessary. Gelatin capsules (00) are then filled to yield the final product.

The tap density of the standardized herbs is 0.95 g/cc each.

Example 19

Gingko Biloba capsules are prepared having the formulation set forth below:

INGREDIENT	mg/capsule
Gingko Biloba Standardized Extract 3.7% gingko flavonone, glycosides; 0.93% gingkolides, less than 5 ppm ginkgolic acid	465 mg
DHA Beadlets (15%)	25 mg
Vitamin B3 (niacinamide)	20 mg

The dry ingredients are mixed and filled into 00 gelatin capsules.

The tap density of the Gingko Biloba Standardized Herb is 0.80 g/cc or higher.

Example 20

Capsules are prepared having the following formulation:

INGREDIENT	Amount/cap
Siberian Ginseng Standardized Herb (0.3% eleutherosides E&B)	160 mg
St. John's Wort Standardized Herb 0.20%	483 mg
Folic Acid	67 mcg
Vitamin B6	2 mg
Vitamin B12	4 mcg
Chromium polynicotinate (0.2% chromium)	40 mcg
Selenium methionine	46.67 mcg

The ingredients are mixed and filled into 00 gelatin capsules. The tap densities of the Siberian Ginseng and St. John's Wort are 0.95 g/cc or greater and 0.75 g/cc or greater, respectively.

Example 21

Capsules were prepared having the following formulation:

INGREDIENTS	Amount/cap
Kava Kava Standardized Herb (11.2% kavalactones	540 mg
Vitamin B6 (pyridoxine)	3 mg
Vitamin B12	6 mcg
Chamomile extract (greater than 1% apigenin)	50 mg
Magnesium ascorbate and/or magnesium oxide	30 mg

The ingredients are dry mixed and encapsulated in 00 gelatin capsules. The Kava Kava Standardized Herb has a tap density greater than 0.87 g/cc or greater.

Example 22

Capsules are prepared having the following formulation:

INGREDIENT	Amount/cap
Valerian Standardized Herb (0.55% valerenic acid)	300 mg

Spearmint flavor	—
Kava Kava Standardized Herb (16.2% kavalactomes)	100 mg
Calcium (as carbonate, citrate malate blend, 34.5% Ca)	100 mg
MgO	50 mg

The dry ingredients are mixed and filled into 00 gelatin capsules. The tap density of each of the standardized herbs is 0.85 g/cc.

Example 23

St. John's Wort capsule is prepared containing 600 mg of St. John's Wort Standardized Herb containing 0.18% hypericins. The tap density is 0.65 g/cc or greater.

Example 24

Ginkgo Biloba capsules were prepared from Ginkgo Biloba standardized herb prepared according to the method of the invention containing 1.9% ginkgo flavonone glycosides, 0.51% ginkgolides, and less than 5 ppm ginkgolic acid. 850 mg of the standardized herb are filled into 00 gelatin capsules. The tap density of the standardized herb is 0.80 g/cc or greater.

Example 25

Capsules are prepared containing 900 mg Panax Ginseng Standardized Herb containing 0.90% ginsenosides. This ingredient is mixed with optional excipients and encapsulated in 00 gelatin capsules. The tap density of the standardized herb is 0.95 g/cc or greater.

Examples 26

Capsules are prepared having the following formulation:

Saw Palmetto Standardized herb (30% total fatty acids)	375 mg
Zinc gluconate	5 mg

Vitamin E (700 IU/g)	30 IU
Stinging Nettle Root (0.8% beta sitosterol)	35 mg

The ingredients are blended and encapsulated in size 00 gelatin capsules. The Saw Palmetto Standardized herb was prepared according to the method of the invention and had a tap density of 0.52 g/cc.

Any number of standardized herb formulations can be prepared utilizing the methods described above.

The processes and products of the present invention address overcome problems associated with whole herb compositions and reduces batch to batch variations can be reduced in this manner, because any differences between batches of raw plant product are also accounted. In essence, one using the method of the invention will be able to have a standardized herb product having a desired marker substance available for use, and dosage forms can be prepared that deliver a consistent and reproducible dose of marker substance regardless of the source of the whole herb, since any variations in marker substance content are accounted for by the method of the present invention.

The foregoing are illustrative of preferred embodiments of the invention and other embodiments will be readily apparent to the skilled artisan and such embodiments are intended to be within the scope of the claims appended hereto.

We claim:

1. A method for producing a standardized botanical comprising:

determining an amount of marker substance to be contained in a botanical product, wherein at least a portion of said marker substance is provided by a botanical material;

determining the amount of botanical material to be contained in the botanical product;

analyzing the content of said marker substance in a sample of said botanical material;

adding a sufficient amount of a dosage modifying material to said botanical material to provide a standardized botanical having the predetermined amount of maker substance.

2. The method of claim 1, wherein said botanical material contains less than said predetermined amount of marker substance and said dosage modifying material is a plant extract containing said marker substance.

3. The method of claim 2, wherein said extract is an extract of said botanical material.

4. The method of claim 2, wherein said extract is an extract of a source different than the botanical material.

5. The method of claim 1, wherein said dosage modifying material is a compound that does not contain any of said marker substance.

6. The method of claim 1, further comprising the step of dividing said standardized botanical into unit doses comprising the predetermined amount of said marker substance and preparing the botanical product.

7. The method of claim 6, wherein said botanical product is a capsule.

8. The standardized botanical product prepared by the process of claim 1.

9. A dosage form comprising the standardized botanical prepared by the process of claim 1.

10. A food product comprising the standardized botanical prepared by the process of claim 1.

11. The method of claim 1, wherein said botanical material is selected from the group consisting of Echinacea purpurea, Panax Ginseng, Siberian Ginseng, Ginkgo Biloba, St. John's Wort, Kava Kava, Valerian officinalis, Saw Palmetto, Black Cohosh, and green tea.

12. The standardized herb prepared by the method of claim 1 having a tap density of from 0.2 to 2.0 g/cc.

13. The standardized herb prepared by the method of claim 1 having a tap density of from 0.6 to 0.9 g/cc.

14. The method of claim 1, further comprising mixing the botanical material/extract mixture with a binder to yield an agglomerate.

15. The method of claim 14, wherein the agglomerate is comminuted such that the resultant particles have a tap density of from 0.4 to 2 g/cc.

INTERNATIONAL SEARCH REPORT

Im tional Application No
PCT/US 99/29186

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 21009 A (FRIEDMAN ELLIOT P ;PHARMAPRINT INC (US); KHWAJA TASNEEM A (US); UN) 29 April 1999 (1999-04-29) page 13, line 20 -page 16, line 10 page 22, line 19 - line 35 ---	1-15
X	WO 97 39355 A (PHARMAPRINT INC ;UNIV SOUTHERN CALIFORNIA (US); KHWAJA TASNEEM A () 23 October 1997 (1997-10-23) page 11, line 25 -page 13, line 16 -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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